

Implementation project for population genetics in 2016

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Population Genomics in 2016

In 2000, the Human Genome project was announced as completed. The \$3 billion dollar endeavor was heralded as ushering in a new era of medical science. This grand announcement was met with excitement, but also skepticism from those in the field of genetics. The manuscript detailing results of the Human Genome Project was published in 2003 (Human Genome Project website). And while many advances have come about since the publication of this data, the “new era of medicine” has not yet been realized. This cutting edge technology has allowed us to sequence the genome, but has outpaced our ability to interpret the information embedded within that sequence. This could be equated to learning to read; we have so far learned the alphabet, but are still learning how to sound out the words. If Genetics is the study of the spelling, origins and functions of individual genes, Genomics could be said to take a broader view, one that encompasses all of an organism’s genes and how they relate to each other, and the environment. One expectation of the Human Genome Project data was that it would revolutionize so called “personalized medicine,” a buzzword in genetics/genomics as well as other medical fields. In 2014 President Barack Obama coined the term “precision medicine.” (PrecisionMed)) “Precision medicine” has no specific definition but encompasses the idea of “the right test/treatment for the right patient/family at the right time.” The office of Public Health Genomics at the CDC headed by Muin Khoury, MD, PhD has spearheaded much of the work in integrating genomic advances into public health initiatives.

The Geisinger Health System in central and eastern Pennsylvania has long been committed to excellent, affordable patient care. Most recently, they instituted the “ProvenCare system,” offering limited refunds for patients unsatisfied with their care. Geisinger was at the forefront of the use of electronic medical records, but went a step further, using the information in an integrative fashion to facilitate research while improving patient care. They created a novel system of research from the EMR that has since been

reproduced by many other centers. (Leader et al 2015). This has include studies looking at environmental risk through population incidence.

In 1968, James Wilson and Gunner Jungner published *Principles and Practice of Screening of Disease* to delineate guidelines for health-related universal screening. (Wilson and Jungner 1968) The central tenants outlined within are the bedrock of our current understanding and practice of universal screens. For population screening especially, all new tests must “pass” these rules set down nearly 50 years ago. These include ideas such as feasibility, cost effectiveness and available intervention. Ingrained in the analysis, Wilson and Jungner note the importance of a “continuing process.” Incredibly the principles still apply to a diverse number of conditions today, from population mammograms to newborn screening. The importance of their treatises is reflected in the fact that current debates on the topic of population screening still recognize the importance of Wilson and Jungner in their discourse.

The field of genomics is relatively uncharted territory, and the ever-shifting and expanding landscape is fraught with ethical and societal challenges which will require evolving strategies to navigate successfully. In this paper, I will explore some of these challenges and how the Geisinger MyCode/GenomeFirst program has developed unique approaches to addressing them, thus shaping the future of precision medicine.

Background

Over the years, genetic testing has become more prevalent, more sensitive, and more broadly based. Karyotype, the ability to look at chromosomes under a microscope to identify structural changes, has been available since the 1960s. This test can identify extra or missing chromosomes, such as the extra copy of chromosome 21 in Down syndrome. A common analogy is that the human genome is a recipe for a human. If one were to imagine the chromosomes as recipe books lined up on a shelf, a karyotype would be like auditing the shelf to see if all the books are there.

In the 1990s, microarrays were developed that were more sensitive than karyotypes and could detect smaller changes in the chromosomes. Continuing the previously analogy, microarray is like opening each recipe book and counting the pages. Missing or extra pages can interfere with the recipe, as missing or extra genetic information can impact (usually deleteriously) human health and development.

One benefit of microarray is that it can screen for many conditions all at once. The increased sensitivity of this test is a double-edged sword, however. In some cases, microarrays are easily interpreted if the deletion or duplication is already well-known and associated with a described syndrome. Commonly, however, microarrays also reveal more variants of unclear significance. While some of these small chromosome variants represent normal human variation, some cause disease, and it is not always easy to differentiate the two. One of the common techniques used to tease this out is testing the parents. If one of the parents has the same genetic change seen in the child, but does not have similar clinical issues, the change is expected to have little or no effect.

As more and more research is done, there is greater appreciation of the spectrum of disorders that can be seen as a result of a single genetic change. Take, for instance the duplication of chromosome 15 at 15q11.2 (Mefford 2012). A common variant found on microarray, it occurs in about 1% of children with

autism . Initially when this variant was identified, parents were tested (although presumably not autistic) and found to also have the duplication, causing geneticists to dismiss the 15q11.2 duplication as a normal population variant. Over time, however, it was found that many of the parents or other family members had subtle symptoms of autism or psychiatric disorders such as bipolar or schizophrenia. The presence of the 15q11.2 duplication does not absolutely mean that disease will develop, but is a risk factor. This is the world of variant interpretation with variable penetrance and expressivity (and something that will keep geneticists employed for a long time). (Richards 2015)

The next phase of genetic testing was and is exome testing. Exomes are the expressed parts of the genome but constitute only about 2-3% of all of our DNA the exome is analogous to the nouns and verbs - the major players that convey the majority of meaning. The whole genome would be all of the words and spaces and sentences in a book as well as the paper itself, cover, etc. There are other important elements in between, but these are still poorly understood by scientists. Whole exome testing allows the clinician to test for virtually every genetic condition at once (with the exception of a few specific categories of genetic disease that are caused by mechanisms other than simple gene misspellings.) But all of us have likely hundreds of variations in our genes. The majority of these have little or no impact, and we are searching for the one that has a large impact –the proverbial needle in a haystack. Despite its technical challenges, whole exome testing has become the test of choice in many circumstances because it is so broad-based.

In addition to its growing use in the clinical setting, exome testing has become one of the more popular means of research testing. Instead of examining one gene at a time, exome testing allows for the analysis of thousands of genes at the same time. If we estimate that the exome contains about 22,000 genes (and we still do not know the exact number), only about 12,000 have known diseases associated. Therefore there are many genes that are still to be discovered. Additionally interaction between genes

can be better studied by looking broadly at a person's genome. And the next iteration of this will be whole genome sequencing, essentially looking at all the information available.

The public health issue with exome/genome testing is that returning results in one person has implications for many other members of that person's family. Similar to the 15q11.2 duplication, a variant might or might not cause disease. It may simply cause increased susceptibility to disease, or late-onset disease. But another family member with the same gene variant could be affected differently.. One long time ethical principle of genetic testing is that minors should not be tested for adult-onset conditions. (Vears 2015) The theory is that the child should be able to give informed consent to be tested for conditions that arise in adulthood.

The all-inclusive nature of exome testing brings with it unintended consequence of identifying genetic changes which cause adult-onset diseases such as cardiomyopathies and cancer susceptibility syndromes. When these mutations are identified, theoretically those results could be masked from children, but importantly these risks could be shared with relatives such as parents. A male child with a BRCA1 mutation causing hereditary breast ovarian cancer is seemingly at low risk for developing these cancers (though other cancers could still arise later in life) but what if it was inherited from a parent, specifically his mother? BRCA1 mutations constitute an approximate 80% risk for developing breast cancer and 50% chance of developing ovarian cancer in a woman's lifetime. There are measures that can be taken to reduce these risks, ranging from well proven screening regimens (for early detection) to prophylactic surgery, which significantly reduces the risk of developing cancer (but unfortunately not 100%).

In 2013, the American College of Medical Genetics and Genomics came out with guidelines stating that, for certain conditions, results should always be made available to the patients regardless of age. (Green 2013) These 'secondary findings' as they were termed, were mostly adult-onset conditions in which

early intervention would ultimately benefit the patient. In general the conditions are associated with cancer or heart disease that manifests in the thirties or later. Many raised concern over this practice, calling it paternalistic to dictate what information patients receive. Proponents argued that genetic test results were not like other test results, and exceptions should be made in the standard results-reporting guidelines. Because of the controversy, in 2014 the guidelines were revised to allow patients to 'opt-out' of receiving these types of results. (ACMG guidelines revision 2014)

While this new guideline was applied to clinical exome testing, it does not extend to research testing. There is ongoing debate regarding "the Common Rule," a staple of current research thinking. Part of the Common Rule states that research participants do not necessarily get back individual test results. Broadly, this rule was adopted because the standards for research and clinical testing are different. But more realistically, returning results to research volunteers is a daunting task. Patients would need to be re-contacted, a clinical visit arranged, etc. But often studies have hundreds if not thousands of patients. In some cases, the results are esoteric and not clinically actionable. In other cases, it might be that the results are not applicable except under specific circumstances. With exome testing a means for research testing reporting these potentially actionable results is one of the ongoing concerns for geneticists and researchers.

Geisinger Health system and MyCode/GenomeFirst

Geisinger Health system is based in central and eastern Pennsylvania and recently expanded to New Jersey as well. There are about 3 million people in the system. Since its founding over 100 years ago, Geisinger developed a reputation for patient-centric care. Additionally, it has emphasized high-quality and affordable care with several novel and innovative systems in place. Nationally, it is renowned for this practice and the institution was able to attract their new CEO from UCLA. Dr. David Feinberg is well

known for patient-centered care as well as being a “servant leader” often giving patients and employees his personal e-mail or cellphone number to follow up((10 things to know about Geisinger's new CEO: Dr. David Feinberg, 2016)). He has pushed the project to be patient-care focused in a manner that is quite different from how most healthcare systems would deal with research. Geisinger was one of the first health systems to adopt EPIC as an electronic medical record and has expanded the role that EPIC plays in not only patient care but research. By encouraging good use of the system, Geisinger has been able to leverage data-mining in many novel methods. ((markerpaper))

MyCode is the population-level health study being done at Geisinger Health System. Patients are consented to study to have an exome test combined with their rich genetic information as a powerful research tool. The uptake of the study has been breath-taking with over one thousand patients consented weekly. Translating the data from the estimated 250,000 research participants to clinical information is something that has not been attempted before. With the Geisinger MyCode system, it was decided to use the ACMG’s recommended list but add on for some additional genes that could have preventative processes in place and to meaningfully let participants know the results for their genetic testing. This process of “genomicly” identifying patients and then changing management is the “GenomeFirst” approach. Importantly this might have more implications for other family members than for the initial person identified.

The other key factor that grew the eventual My Code project was teaming with a pharmaceutical company called Regeneron Pharmaceuticals. Regeneron had some success with new methods of drug development; rather than traditional small molecules, they created medications based on antibody properties. This method has proven to be faster to develop, have somewhat reduced side effects and, in the limited clinical studies, proven to be effective. Regeneron was looking to develop novel drug targets by looking at genetic risk and well-curated clinical characteristics, something that the Geisinger Health System was uniquely able to provide. Regeneron has had immense recent success following the

discovery of a gene associated with familial hypercholesterolemia called *PCSK9*. (Stein 2012). They created the first novel therapy for elevated cholesterol in over 30 years- a class of drug that is estimated to be worth over \$1 billion dollars.

Another important feature of GenomeFirst is what is termed “just in time” information. The traditional medical model stipulates that the patient only have the test done that they are interested in. For example, if you want to know how a patient would potentially react to a medication you may consider how they reacted to a smaller dose or similar medication. If you were to use pharmacogenomic testing (genetic testing related to medication action or metabolism) to guide treatment it could be ordered, but this inherently creates a delay in use. With “just in time” testing for pharmacogenomics for example, the relevant genetic information would be present in the background of the EMR but when you triggered the system by ordering a medication on the list, it would immediately pull the information for reference. Pre-emptive testing is only possible and time and cost effective when the test can be picked up within the context of other testing or as part of a broader panel.

The Geisinger patient population also uniquely allows for the use of well-defined family data to aid in interpretation of novel genetic variants identified by MyCode. Linkage analysis is a tool that has been used for decades by geneticists to find genes of interest. (Staples 2015) Using a new computational tool called Primus it is possible to link multiple MyCode participants together and determine their degree of relationship. It is therefore possible to create linkage pedigrees just based on available information, without relying on patient-reported information. The advantage is that by looking at the intersection of objective data points, say the presence of a change in a breast cancer susceptibility gene in several women and the incidence of breast cancer in that population, it might be possible to elucidate if that genetic change is a contributing factor. But importantly, the negative is also informative- say someone has a sister with early onset breast cancer and her sister has a variant that is of unknown significance. If one sister does not have a history of breast of cancer without the variant and another sister does have

breast cancer with the variant, it is possible to infer that the variant may link to be causative. This does not prove to the variant's pathogenicity but it provides more evidence. Going out further in the family may even provide more information and this has been proven with the MyCode project.

A national program called the Precision Medicine Initiative (PMI) has taken center-stage with political capital and, importantly, funding available to implement it. The project, launched in early 2015, aims to leverage the advancements made in genomics, bioinformatics and health information to aid in discovery and "precision" healthcare. It was a significant strategic goal for the Obama Administration. Furthering efforts started in the Electronic Medical Records and Genomics (EMERGE) network and Clinical Sequencing Exploratory Research (CESR) grants, the PMI hopes to establish a repository of one million (or more) samples with extensive associated biological data. Geisinger is poised to play a very crucial role in this process, given the already impressive recruitment to date, and the fact that many of the planned initiatives for the PMI have already been implemented at Geisinger.

<i>Wilson and Jungner Classic Screening Criteria</i>
<ol style="list-style-type: none"><i>1. The condition sought should be an important health problem.</i><i>2. There should be an accepted treatment for patients with recognized diseases.</i><i>3. Facilities for diagnosis and treatment should be available.</i><i>4. There should be a recognizable latent or early symptomatic stage.</i><i>5. There should be a suitable test or examination.</i><i>6. There should be acceptable to the population.</i><i>7. The nature history of condition, including development from latent to declared disease, should be adequately understood.</i><i>8. There should be an agreed policy on whom to treat as patients.</i><i>9. There cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.</i><i>10. Case-finding should be a continuing process and not a “once and for all” project.</i>

In multiple publications since 2009, the CDC Office of Public Health genomics has classified conditions in which genomic and family history have a base of synthesized evidence supporting implementation into practice. Using various sources including national panels, the US Preventative Taskforce (USPTF) and Evaluation of Genomic Applications in Practice and Prevention (EGAPP) recommendations, among the three most well described are Familial hypercholesterolemia (FH), hereditary breast and ovarian cancer (HBOC) and Lynch syndromes (hereditary susceptibility to colorectal and other cancers.) These disorders are specifically noted as they are autosomal dominant (meaning all first degree relatives are at 50% risk)

and importantly have well established guidelines for management. Collectively, using approximations based on incidence, these three disorders will be found in around 1-2% of the general population. It is also widely cited that the current incidence rates are likely too conservative and may be underestimating the true population incidence. These disorders additional cross ethnic, social and economic boundaries.

Fundamentally, our current understanding of these conditions comes from the inherent bias of a personal or family history of disease. These bias all subsequent observations, screens and interventions. There is a bias toward pathogenicity since genetic testing currently requires a sufficient personal or family history of cancer to justify test usage. For example, Lynch syndrome screening often starts with tumor testing and subsequent family history information gathering. The variability in penetrance and expression are more difficult to gauge in the general population.

One strategy to combat these disorders is universal population screening. Universal screening does have the advantage of inclusion but may miss those patients that would develop disease prior to normal age screening (for example breast screening starting at age 40, colonoscopy starting at age 50 and lipid screening around age 8). Universal screening also accepts a bias toward false positives in order to reduce false negatives with considerable health care expenditures and personal anxiety as a result. This specific tension is well noted in the USPTFs repeated attempts to change breast cancer screening and the public's anxiety with doing so. Universal screening has also shown to be an area with significant health disparity (Belasco 2014).

While population-level genomics is in its infancy, the thought processes are becoming more clearly aligned with the principles set forth by Wilson and Jungner. The cost of genomic testing has decreased and the infrastructure to handle the complex results has increased, a testament to forward thinking in the genetics/genomics community (though there is still a considerable way to go). From the ACMG's list

of secondary findings to leadership from the CDC Office of Public Health Genomics, a framework for screening processes has been developing. The possible general application of exomes is not as far-fetched as once thought, and programs such as the GenomeFirst at Geisinger Health System and the upcoming Precision Medicine Initiative will provide important information about the viability of such systems.

One important difference between current universal screening (essentially secondary prevention) and genomic screening is the allowance for primary prevention of the disease state. For FH and HBOC, there are well established management guidelines to alleviate the disease burden in the affected group. For FH, aggressive use of cholesterol lowering therapies and screening for atherosclerosis can be primary prevention of myocardial infarction or strokes. Those with FH typically have their first cardiovascular event in their 30s or 40s. Additionally, mitigating other risk factors such as diet, diabetes or hypertension may be more aggressively pursued for those with FH. In the case of HBOC, national guidelines note the value of prophylactic mastectomy and oophorectomy in the high risk population. While neither will fully eliminate the risk, it does significantly reduce the risk. There is also use of prophylactic medications such as tamoxifen and reducing estrogen exposure with oophorectomy reducing the risk for breast cancer. One could also make the argument that colonoscopy with polyp removal could be considered primary prevention in Lynch syndrome. Early detection of cancer results in improved health outcomes in HBOC and Lynch syndrome. MRI of the breast is well established in those with HBOC but is too costly as a general population screen. Another advantage of genomic screening might be that it would allow aggressive screening to be targeted to a very specific increased-risk population (MRI of the breast is well established to result in improved health outcomes in HBOC and Lynch syndrome, but is too costly as a general population screen) while utilizing universal screening to focus better on an older population with sporadic disease and reduce false positives (mammograms are

especially difficult in younger women and result in more unnecessary biopsies) thus better utilizing healthcare dollars..

There are still many hurdles to the use of genomics for population screening. While cost have significantly reduced, the feasibility of coverage is difficult to justify at this time. More studies need to be done looking at the economic ramifications. It has taken many years to show the economic value with tumor screening for Lynch syndrome but the evidence is quite substantial now; and interestingly the cost-analysis included cascade testing in other family members, which would also be available with genomic screening. {Gudgeon 2011}

While the infrastructure to manage these conditions is there currently, increasing the population that needs to be screened will likely be a burden to the current system. There is a significant shortage of trained genetic professionals, and other types of medical professionals may not be prepared to handle the added burden of management for FH, Lynch and HBOC without further guidance. This is not an unprecedented undertaking and the right means and education could be done with professional societies to bridge this gap. Along the same lines, insurance coverage for screening would have to be updated but economic/societal benefit would aid in demonstrating its long-term value to insurance companies and the public.

There is a fundamental question that needs to be addressed as well: does identification of a pathogenic variant give the diagnosis alone? Discovery of deleterious mutation should not constitute diagnosis of that condition. On one level, from the patient perspective, discovery of a BRCA mutation does not mean that the patient has cancer; only that they are at significantly increased risk of developing cancer. This is not a minor point in return of results. Most current clinical criteria are designed to look at the likelihood of having a mutation, often in those already identified with disease. For example, the various criteria for FH all include a current diagnosis of hypercholesterolemia plus other factors. Some even include the

identification of a genetic variant. The Lynch criteria often emphasize the family history and tumor testing in an affected patient. There are various breast cancer programs available that look at the multitude of breast cancer risks. But what of patients who have not yet had manifestation of disease? Simplistically this occurs in cascade testing from affected patients to their relatives. And it is this very population that underscores the value of genomic testing: identification and prevention prior to disease development. But these are also families that have a history of cancer and therefore maybe other shared traits (genetic, environmental, and behavioral) that contribute to this “familial” risk.

Racial and socioeconomic differences in the early adoption of genomics may exacerbate existing health disparity. Because most participants in genomic research to date have been Caucasian, those of non-Caucasian backgrounds are still likely to be underdiagnosed because of a lack of identification of unique pathogenic variants in that population. For example, in BRCA, while there have been laudable improvements in reducing the number of variants of uncertain significance, those of minority backgrounds are still twice as likely to have a variant of uncertain significance as those of Caucasian background. This is also an opportunity for universal screening to improve the landscape of genomic healthcare; better characterization of variants will occur with more information. A similar phenomenon has occurred with newborn screening for Fabry disease in Japan (Inoue 2013). This is a disorder that can have quite variable manifestations and the screening done in Japan has been important in helping better understand the disorder.

One of Wilson and Jungner’s criteria is especially salient in the discussion of genomic screening: “case findings should be a continuing process and not a ‘once and for all’ project.” The process of genomic screening will be re-iterative and a learned process that will better be able to clarify some of the questions raised. Like newborn screening there will need to be integrated education, testing, clinical services and program management. The evidence will also need to be provided for clinical utility in addition to clinical validity. The program should be an opt-in as to ensure informed choice, confidentiality

and respect for autonomy. And along those same lines, there should not be discrimination against those who choose to opt-out especially a concern as health plans create incentives for accepted screening.

Ethical issues

The ethical issues of such a complex study are quite myriad. Starting at the beginning with a fundamental question impacting much of clinical research today: how often are patients being properly consented? Informed consent for complex genetic information is quite difficult with nuanced language and complex concepts such as DNA and understanding of risk (e.g. 1.3 relative risk, 30% increased risk, 30% absolute risk). Additionally, the MyCode study is primarily being funded through a pharmaceutical company whose fervent hope is that they will discover some drugs to develop from this novel approach. In the wake of the outcry regarding Henrietta Lack and HeLa cells, the balance must be properly structured for patient autonomy/research.

The nature of MyCode study was that patients were consented at least 8 years ago. We wondered how many remembered that they were enrolled in a study. Anecdotally, we have seen that patients do not remember, because they have tried to sign up again for the same study. Additionally, from a researchers perspective, the consent has changed and many patients will have to have be re-consented in order to update their knowledge and expectations. The entire release of results in such a broad manner is not specifically been done in other large study populations, and the return of results portion of the MyCode project will be quite informative to the genomics community at large.

There are some clear weaknesses in the Geisinger MyCode study. The most oft cited is the lack of racial diversity. The strength of a stable population also reflects a fairly homogenous Caucasian population. This is a significant and on-going struggle in large genetic studies. Going back to genome wide association studies, similar criticisms were made that those groups do not reflect the general US population (let alone the world population). Geisinger is increasing its reach with the annexation of new

health care systems, but this will only slightly change the challenging demographics. Similarly, the socio-economic diversity is also not typical, however unlike many other genomic populations, the Geisinger population is skewed to slightly less educated and less wealthy than the average US population. The population also skews significantly older, again reflecting the area. This however may be a strength for genetic findings (though perhaps a weakness for genetic intervention). If a concern is penetrance of a disorder, an older population better reflects those truly affected by a genetic change. A younger population would not give information about whether a person would develop disease in the future (though with the long term longitudinal nature of this study it should be picked up eventually).

Another limitation is the data available from the EMR. While the data quality is quite long as a strength, it is difficult to assess the quality of the data as there is no objective criteria available. Certainly the person who has only a limited number of encounters with the healthcare system will provide less information than the person followed for many decades. But there are likely limitations as to what is entered into in the EMR as well. Documentation certainly can contain errors but also accidental and presumptive information as well. Geisinger has also been at the forefront of a movement to have records fully open to patients and is implementing something called the “shared note” where patients and providers together create the documentation for an encounter.

Geisinger is specifically a community hospital, albeit on a scale that makes it an exception as a non-university system. Comparable hospitals such as Cleveland Clinic and Mayo Clinic have very different focuses of care, often at the cutting of practice rather than at the cutting edge of care. However a key part of what is being done at Geisinger is specifically designed to be replicable. The genomics program as well has been set up to be scalable even with a smaller genomics presence and in anticipation of reducing technology costs. By starting in a research setting, Geisinger can show the value for care, increasing acceptance importantly by insurance companies and the government services.

Application of the Wilson and Jungner Criteria should continue to be strongly associated with the exciting developments in population genomics. We should heed the warning laid out by this omniscient pair of Wilson and Jungner 48 years ago:

“The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, to bringing treatment those with previously undetected disease, and on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy.”

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